REMARKS

Specification

The Specification has been amended at page 1 as requested by the Examiner [Office Action, page 2, Section 6] to reflect the priority status of U.S. Applications 09/177,776 and 09/178,115.

Claim Objections

Claim 31 has been amended according to the Examiner's directive at page 2 of the Office Action, such that items "(1)", "(2)" and "(3)" have been re-numbered as "(i)", "(ii)" and "(iii)".

Applicants respectfully submit that no new matter has been entered by the above amendments to the pending claims, and respectfully request entry of the above amendments and reconsideration of the application as amended.

35 U.S.C. Section 102(b) Rejection

Claims 31-32, 34, 37-39 and 41 stand rejected under 35 U.S.C. Section 102 (b) as "being anticipated by Zavada *et al* (Int. J. Oncology 1997; 10:857-863, previously cited) . . . for the reasons of record. . . . " [Office Action, Section 7, page 3.] The Office Action maintains that Zavada et al. 1997 teach a cellular adhesion assay which comprises the same steps and limitations as the claimed assay, and that also teach a method

of identifying molecules that bind specifically to a site on the MN protein, to which cells adhere.

Applicants respectfully traverse and submit that the cellular adhesion assay of Zavada et al. does not anticipate the instant inventive method for a number of reasons, including that the Zavada et al. assay:

1) does not teach **each and every limitation** of the claimed assay;

2) does not enable how to identify the **cell adhesion site** of **native** MN protein;

3) does not enable how to **correctly** identify molecules that bind to the **cell adhesion site** of **native** MN protein; and

4) does not enable how to **correctly** identify molecules that inhibit the binding of cells to the **cell adhesion site** of **native** MN protein.

Whereas Zavada et al. 1997 teaches away from the cell adhesion site being within the proteoglycan-like domain (PG domain) of the MN protein, the instant application correctly identifies the cell adhesion site as being within the PG domain. Further, in contrast to Zavada et al. 1997, the instant application enables how to identify molecules that are capable of binding to **the cell adhesion site** of **native** MN protein, and of inhibiting cell binding to **native** MN protein, which molecules are considered to be therapeutic.

I. Zavada et al. 1997 Assay Limitations Different

First, Applicants respectfully submit that the cellular adhesion assay of Zavada et al. 1997 did not teach **each and every limitation** of the claimed assay, pointing out that the "MN protein" used in the cell adhesion assay of Zavada et al., 1997 is not the same as the "MN protein" defined in claim 31, the only independent claim of the instant invention. The Zavada et al. 1997 so-called "MN protein" used in the cell adhesion assay was not encoded by SEQ ID NO: 1 (or any of the other sequences defined by claim 31), but was an affinity purified **fusion protein** pGEX-3X-MN originally described in Zavada et al., Int. J. Cancer, 54: 268-274 (1993) [see Zavada et al. 1997, page 858, 2nd col, "Adhesion assay": "For adhesion assay . . . , 25 µl aliquots of MN protein (affinity purified pGEX-3X MN) . . . or of control proteins were spotted on 5 cm diameter bacteriological Petri dishes and allowed to bind for 2 h at room temperature." (References omitted.)]

It was because of the difficulty of purifying MN protein that the inventors had originally used the GST-MN fusion protein in the 1997 Zavada et al. cell adhesion assay. As pointed out in the instant specification at page 68, it is not a trivial matter to purify transmembrane proteins like MN protein for purposes of testing cell adhesion:

> Purification of transmembrane proteins like MN/CA IX often poses technical problems because they tend to form aggregates with other membrane proteins due to their hydrophobic TM segments. To avoid this, we engineered truncated MN/CA IX ΔICΔTM, which is secreted into the medium. Indeed, truncated MN/CA IX was obtained in higher purity than MN/CA IX+. Unfortunately, this protein was of little use for our purposes, since it was inactive in the cell adhesion assay. Such a situation has also been described for other cell adhesion molecules: their shed, shortened form either assumes an inactive conformation, or it adsorbs to hydrophobic plastic "upside down," while complete proteins adsorb by hydrophobic TM segments in the "correct" position.

[Instant application, page 68, lines 23-32.]

The pGEX-3X-MN fusion protein comprises a portion of the MN protein fused with the 26 kDa C-terminus of glutathione-S-transferase ["the GST anchor"] in the pGEX-3X vector [Pharmacia], which fusion protein was further characterized in Zavada et al., U.S. Patent No. 5,387,676 ["the '676 patent"], and has a much higher molecular weight than the MN protein. As shown in Figure 2 of the '676 patent, the recombinant MN protein expressed from the pGEX-3X vector and identified by autoradiography in column B, using ^{125}I-labeled Mab M75, represented several species, with a range of molecular weights, the largest protein being about 80 kDa, which is significantly different from either of the "twin protein(s)" of **native** MN

protein (54-58 kDa) or the MN protein oligomers of 153 kDa identified by M75 Mab in cellular extracts.

The instant application explains why Zavada et al. 1997 **taught away** from the cell adhesion site being within or near the PG domain and incorrectly identified the M75 Mab as not binding to the MN's cell adhesion site and not inhibiting cells from binding to MN protein. **Zavada et al. 1997 "did not realize that GST anchor itself contains another binding site, which is not blocked by M75 [Mab]." [Instant specification page 68, lines 12-13.]** The instant Specification points out that Zavada et al. 1997 was incorrect as follows:

> There can be no doubt on the specificity of cell attachment to purified MN/CA IX+ [complete MN protein]. It is abrogated by specific MAb M75, at a dilution 1:1000 of ascites fluid. **This is a correction to our previous report in Zavada et al., Int. J. Oncol., 10: 857 (1997)** in which we observed that MN/CA IX produced by vaccinia virus vector and fusion protein GST-MN support cell adhesion, **but we did not realize that GST anchor itself contains another binding site, which is not blocked by M75.**

[Instant Specification, page 69, lines 8-13; emphasis added.]

As explained above, it is clear that Zavada et al. (1997) using the MN **fusion protein**, pGEX-3X-MN, taught away from the cell adhesion site being within or near the PG domain of the MN protein and did not enable cell adhesion assays that could

correctly identify molecules that bind to MN's cell adhesion site within the PG domain and that inhibit the adhesion of vertebrate cells to MN protein. Applicants respectfully point out that it was not until the inventors used the complete MN protein expressed from MN cDNA in Vero cells from vaccinia virus and purified on sulfonamide-agarose, and not until the MN cell adhesion site was identified, that the instantly claimed invention was enabled.

II. Zavada et al. 1997 Assay Not Enabled for Identifying the Cell Adhesion Site of Native MN Protein

Secondly, in order to serve as an anticipating reference, a reference must be enabling. The Manual of Patent Examining Procedure (MPEP) clearly points that out in Section 2121.01 [MPEP 2121.01] which reads:

> In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'. . . . *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). . . . **The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter**. . . .

[Emphasis added.]

At the time of Zavada et al. 1997, the location of the cell binding site in the MN protein **was not known**. There is

nothing in Zavada et al. 1997 that identifies the location of the cell binding site of the MN protein; in fact, the assay described in Zavada et al. 1997, **taught away from** the cell adhesion site of the MN protein being within or near the PG domain. Zavada et al. 1997 reported that the one molecule -- the M75 Mab, which binds an epitope within the PG domain of the MN protein -- that should have inhibited cell binding to the MN protein, if the cell adhesion site was within or near the PG domain, did not inhibit cell adhesion to the MN fusion protein. Without knowledge of the location of the cell adhesion site within the MN protein, one of skill in the art would not be able to confirm the binding of a compound specifically to the MN cell adhesion site, which property is necessary for utility of the claimed assay.

III. Zavada et al. 1997 Assay Not Enabled for Correctly Identifying Molecules that Bind to the Cell Adhesion Site of Native MN Protein, or that Inhibit the Binding of Cells to the Cell Adhesion Site of Native MN Protein

The Examiner states that the assay of Zavada et al. 1997 identifies a molecule, the M75 monoclonal antibody, that does not inhibit cell binding to a protein, and therefore anticipates the screening assay of the instant invention. However, the assay of Zavada et al. 1997 was used solely to determine whether the MN protein is a cell adhesion molecule.

The instant application discloses making a critical finding that is **in direct opposition to the report of Zavada et al. 1997**, that is, that the instant application identifies by the instantly claimed methods that the M75 Mab is a molecule that **does** inhibit cell binding to native MN protein or MN polypeptide. Native MN protein is a different protein than the pGEX-3X-MN fusion protein of Zavada et al. 1997. The assay of Zavada et al. 1997 is clearly a **different assay from the claimed assay**, as it had a different purpose, used a different protein to test for cell adhesion, and gave different results for the M75 Mab.

The assay described in Zavada et al. 1997 not only was not designed to identify the molecules identified by the instant invention, but **taught away from** the one molecule (the M75 Mab) that should have inhibited cell binding to the MN protein, if the cell adhesion site was within or near the PG domain. The assay of Zavada et al. 1997 was both **not designed to**, and **was not enabled to** correctly identify molecules that bind the cell adhesion site of MN protein, or to correctly identify molecules that were capable of inhibiting cell binding to the MN protein.

The present invention describes a method of screening potentially therapeutic molecules, both organic and inorganic, for a desirable property, namely, the ability to prevent cells from binding to the MN protein, which property can be useful in

treating preneoplastic/neoplastic disease. The assay of Zavada et al. 1997, on the other hand, used different elements, had a different purpose, incorrectly identified the M75 Mab as a molecule that would not inhibit cell adhesion to MN protein, and would have identified a different set of molecules, if it had been used as a screening assay.

Further, in order to serve as an anticipating reference, the cited art must provide an enabling disclosure teaching one skilled in the art to practice the claimed invention. [MPEP 2121.01, supra.] Since Zavada et al. does not enable the claimed methods, but teaches away from the claimed methods, it cannot be anticipatory prior art against the claimed invention, nor for that matter, can it render the claims obvious.

Applicants respectfully conclude that Zavada et al. 1997 does not anticipate or render obvious the claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 U.S.C. § 102(b) rejection in view of the above remarks.

35 U.S.C. Section 112, First Paragraph Rejection

Claims 31-39, 41 and 42 stand rejected under 35 U.S.C. Section 112, first paragraph, because

> . . . [which cell line] must be known and readily available to the public or obtainable. . . . If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cell line. . . .
>
> . . . However, all of the required terms of the deposit under the Budapest Treaty have not been clearly defined in the specification.

[Office Action, section 9, pages 6-7.]

Applicants respectfully respond that the hybridomas VU-M75 and MN 12.2.2 were deposited at the American Type Culture Collection (ATCC) under ATCC Nos. HB 11128 and HB 11647, respectively, under provisions that satisfy the requirements of 37 CFR 1.801-1.809. Applicants respectfully point out that the instant application states at page 74, lines 4-11, that the deposits of VU-M75 and MN 12.2.2 were

> made under the provisions of the Budapest Treaty on the International Recognition of Deposited Microorganisms for the Purposes of Patent Procedure and Regulations thereunder (Budapest Treaty). . . . The hybridomas . . . will be made available by the ATCC under the terms of the Budapest Treaty, and <u>subject to an agreement between the Applicants and the ATCC which assures unrestricted availability of the deposited hybridomas . . . to the public upon the granting of patent from the instant application</u>.

[Emphasis added.]

Enclosed as Appendix A are copies of the ATCC Deposit Receipts which indicate that the hybridomas VU-M75 and MN 12.2.2, which produce antibodies M75 and MN12, respectively, were deposited under the terms of the Budapest Treaty on September 17, 1992 and June 9, 1994, respectively. The Manual of Patent Examining Procedure (MPEP) states at the end of Section 2410.01 under the heading "Conditions of Deposit," that

> the mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty would satisfy all conditions of these regulations except the requirement that all restrictions on access be removed on grant of the patent. *Ex parte Hildebrand,* 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

As the last sentence of the above-quoted paragraph of the instant application indicates, the Applicants stated that their agreement with the ATCC "assures unrestricted availability of the deposited hybridomas . . . to the public upon the granting of patent from the instant application."

However, to provide further assurance that all the requirements concerning the hybridoma deposits are met, the undersigned Attorney for the Applicants states:

> By signing below the Attorney for the Applicants certifies that:
>
> > (a) during the pendency of this application, access to the deposits of the hybridomas VU-M75 and MN 12.2.2, deposited at the American Type Culture Collection (ATCC) at 12301 Parklawn

Drive, Rockville, MD 20852 (USA) under the ATCC designations HB 11128 and HB 11647, will be afforded to the Commissioner upon request;

(b) all restrictions imposed by the depositor on the availability to the public of the hybridomas VU-M75 and MN 12.2.2 will be irrevocably removed in accordance with 37 CFR 1.808 upon the granting of a patent from the instant application;

(c) the deposits of the hybridomas VU-M75 and MN 12.2.2 will be maintained in the ATCC for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited hybridomas, whichever is longest;

(d) the deposits of the hybridomas VU-M75 and MN 12.2.2 will be replaced if they should become nonviable or non-replicable; and

(e) the deposited hybridomas VU-M75 and MN 12.2.2 are identical to the biological materials described in the specification and that were in the applicants' possession at the time the application was filed.

Applicants respectfully conclude that the deposits of hybridomas VU-M75 and MN 12.2.2 at the ATCC under the terms of the Budapest Treaty in view of the above-quoted statements is sufficient to meet all the requirements of deposit imposed by 37 CFR 1.801-1.809, and that the above statements by the undersigned Attorney for Applicants leave no doubt that those

requirements have been met. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 U.S.C. § 112, first paragraph rejections of claims 31-39, 41 and 42.

35 U.S.C. Section 103(a) Rejection [Sections 10-12 of Office Action)

Common Ownership (Section 11 of the Office Action)

The Office Action states at page 8 that "Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a)." [Office Action, page 8, Section 11.]

Applicants are respectfully aware of their duty under 37 CFR 1.56 concerning reporting lack of common ownership of any claimed aspects of the invention at the time it was made. Applicants respectfully declare that the invention as claimed was commonly owned at the time all claimed aspects were made.

35 U.S.C. 103(a) Rejection

Claims 31-32, 34, 37-39 and 41-42 stand rejected under 35 U.S.C. Section 103(a) as being "unpatentable over Zavada et

al. [Int. J. Oncology, 10: 857-863 (1997)]. . . ." [Office Action, Section 12, page 8.] Applicants most respectfully but most emphatically traverse, relying upon the detailed reasoning of the above response to the 102(b) rejection over Zavada et al. 1997. Since Zavada et al. 1997 teaches away from the instantly claimed methods, Zavda et al. 1997 cannot render the instantly claimed methods obvious.

The Office Action further states that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use human cells in place of the NIH 3T3 cells used by *Zavada* et al." [Office Action, page 9.] Applicants respectfully respond that using human cells instead of mouse cells in the assay described in Zavada et al. 1997 would not have changed the teachings of Zavada et al. 1997 and would not have provided enablement for an assay to screen for molecules that inhibit cell adhesion to the MN protein.

As Applicants explained above, the M75 Mab did not prevent NIH 3T3 mouse cells from binding to the MN fusion protein pGEX-3X-MN of Zavada et al. 1997 because of inherent properties of that MN fusion protein. Analogously, the M75 Mab would not have prevented the binding of **human cells** to that GST-MN **fusion protein**, as the **"GST anchor itself contains another binding site, which is not blocked by M75."** [Instant specification, page 69, lines 11-12; emphasis added.] Human

cells would still have bound the MN fusion protein of Zavada et al. 1997 at the GST portion of the fusion protein, in both the presence and absence of the M75 Mab.

More specifically, the Examiner states that

> [o]ne of skill in the art would therefore be **motivated to use HeLa cells** as a part of the instant method **because it possessed an endogenous source of the MN protein** from which it is possible to screen for molecules that are capable of being inhibited by a test compound and by using HeLa cells, it would more closely model affects of a test compound on a human.

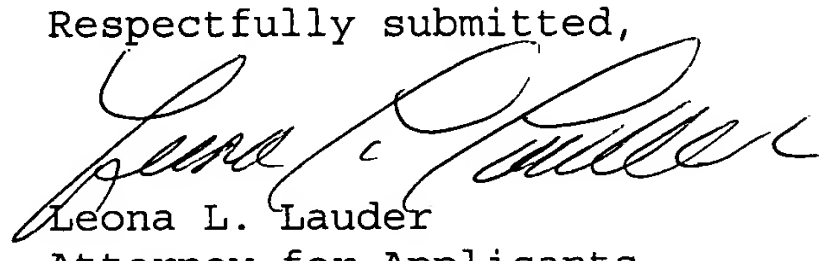
[Office Action, page 9, Section 12; emphasis added.] Applicants respectfully submit that Zavada et al. 1997 taught that the degree of cell adhesion did not correlate directly with MN protein expression. Whereas CGL1 cells (nontumorigenic cells that do not strongly express MN protein) and HeLa cells "adhered to MN protein, ... CGL3 cells, strongly expressing MN protein, adhered less efficiently to MN protein dots than CGL1." [Zavada et al. 1997, page 861, 1st col, last paragraph.] Since Zavada et al. 1997 teaches that cell adhesion did not correlate with MN expression, or the lack thereof, the skilled artisan would not be motivated to use MN-expressing HeLa cells (which potentially bound MN protein dots less efficiently) in a test to measure inhibition of cell adhesion to MN fusion protein. Zavada et al. 1997 then *taught away* from using human cells that strongly expressed MN protein in the Zavada et al. 1997 assay.

As explained above in detail in the response to the 102(b) rejection, Zavada et al. 1997 teaches away from the instantly claimed invention. Zavada et al. 1997 cannot then render the instantly claimed invention obvious. Applicants respectfully request that the Examiner reconsider the instant 103(a) rejection in view of the above remarks, and withdraw this rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claim amendments be entered, and that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



Leona L. Lauder
Attorney for Applicants
Registration No. 30,863

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